BAMC/WHMC
PROTOCOL FOR CLINICAL INVESTIGATION – EXPEDITED

1.0 Title: A Comparative Study: ImPACT MIL versus ANAM4™ TBI MIL for Acute Concussion

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4.0 Research Plan

4.1 Purpose:

The study's purpose is to evaluate the differences in clinical utility and effectiveness between the Automated Neuropsychological Assessment Metrics 4th edition Military Version (ANAM 4 TBI MIL) and the Immediate Post-Concussion Assessment and Cognitive Testing Military Version (ImPACT MIL), which are both designed to determine the effect of mild traumatic brain injury (mTBI) on neurocognitive functioning. Since a decreased ability to maintain balance is also a characteristic of mTBI, the Unipedal Stance Test (UPST) will be given as a measure of potential neurological impairment, and compared to the traditional neurocognitive tests. Another proposed indicator of the presence of brain injury after mild head

trauma is a quantitative electroencephalogy (QEEG), which will be also given as an additional measure using a portable EEG monitoring device, the AHEAD M-100.

4.2 Hypotheses/Research Questions:

A. To what extent do individuals diagnosed with mTBI differ from otherwise healthy, non-injured individuals on the ANAM4 TBI MIL and ImPACT MIL?

B. Does either neurocognitive assessment battery demonstrate significantly greater sensitivity and specificity for an acute concussion in a military sample?

C. To what extent do individuals diagnosed with mTBI differ from otherwise healthy, non-injured individuals on the Ahead M-100 device using the manufacturer's proprietary interpretive algorithms?

D. Does the use of the Ahead M-100 demonstrate significantly greater sensitivity and specificity for an acute concussion in a military sample when compared to traditional neurocognitive measures?

4.3 Significance:

Mild TBI can be found in both the civilian and military environments. Common causes of TBI, both civilian and military, include falls, motor vehicle accidents, striking or being thrown against an object, and assault. According to existing data, more than 1.5 million people experience a traumatic brain injury (TBI) each year in the United States. These injuries have been identified as possibly causing long-term or permanent impairments. In addition to the growing population of the injured, mTBI costs the nation nearly $17 billion each year in funding (Binder, 2003). Accurate neurocognitive assessment calculated by a valid, sensitive, specific, computerized instrument would greatly assist in the medical care of concussed patients. A rapid test that shows strong validity and utility will provide the capacity for assessment in remote locations that lack neuropsychological services.

4.4 Military Relevance:

The army is currently using two different computerized neurocognitive batteries for measuring concussion: ANAM4 and IMPACT. Both tests have their advocates and detractors, but there is no data as to which is superior for this purpose. This study will allow the Army to best serve its service members by selecting the superior instrument for wider fielding and use.

Management of acute concussion is a significant problem for the military today. As an alternative to traditional neuropsychological testing, which can only be conducted by a licensed clinical neuropsychologist, automated (computerized) neurocognitive testing has been proposed for the assessment of cognitive impairment in individuals who are suspected to have mTBI/concussion. It is known that mTBI often does not present with apparent visible symptoms, and the symptoms may also overlap with other diagnoses; therefore, the most effective test needs to be chosen to aid in the detection and treatment of mTBI. Additional benefits would include the means to monitor the injured soldier's status, treatment progress, and return-to-duty potential. The study seeks to establish which of the tests currently in use by the military has the strongest validity and utility for soldiers suffering from mild traumatic brain injury (TBI) is considered the

Table 1.
Common Symptoms of Traumatic Brain Injury

General Symptoms of TBI	Symptoms of Moderate to Severe TBI
Headaches	Loss of consciousness (30 minutes or more)
Difficulty organizing daily tasks	Personality change
Mental confusion (easily confused, easily feeling overwhelmed)	Loss of coordination
Lightheadness or feeling dizzy	Weakness or numbness in the extremities
More sensitive to auditory stimuli, lights, or other distractions	Slurred speech
Behavior or mood changes (feeling sad, anxious, or listless)	Dilation of one or both pupils
Double vision, blurred vision, or tired eyes	Inability to awaken
Ringing in the ears	Seizures
Bad taste in the mouth	Repeated vomiting or nausea
Fatigue or lethargy (feeling tired all of the time)	A severe, persistent, or worsening headache
A change in sleep patterns	
Trouble with memory, concentration, or calculations	
Easily irritated or angered	
Impulsivity (lack of inhibition)	
Slowed movement, talking, reading, or thinking	
Sexual dysfunction	

signature wound of the current conflicts (Okie, 2005; Keltner, 2007). As of September 30, 2007 the Pentagon listed 4471 TBI diagnoses from OEF and OIF. However, the founder of the Congressional Brain Injury Task Force, estimates more than 150,000 instances of TBI have occurred among approximately 1.5 million OEF/OIF participants (Zoroya, 2007). The discrepancy may be due to the idea that an estimated 80% of TBIs are mild (mTBI); a condition that is not readily apparent (Heegaard, 2007). Most mTBI patients make a rapid recovery, suffer few post-injury complications, and, for these reasons, often bypass acute medical attention or

hospitalization. Nevertheless, between three to five percent of mTBI patients develop chronic symptoms, and delayed symptom onset is not uncommon (McCrea, 2008).

In OEF and OIF, the most common sources of TBI are explosives and blasts (Keltner 2007; DePalma, 2005; Finkel, 2006; and Warden 2006). Traumatic brain injury accounts for approximately 60% of war injuries caused by blasts (Keltner, 2005). The severity of the TBI depends on the magnitude of symptoms that result from the injury, and outcomes can range from a complete recovery to permanent disability or death (Rao, 2000; Heegaard, 2007; Moppett, 2007). When blasts and other mechanisms of injury that result in loss of consciousness produce a TBI, the injury may be defined as mild (≤ 30 minutes) (American Congress of Rehabilitation Medicine definition). Also accompanying TBI may be anterograde memory loss or post-traumatic amnesia, as well as difficulty encoding new information following the injury. Not all TBI victims suffer from loss of consciousness or amnesia. Those with more mild exposure to trauma may become dazed and confused, characterized by difficulties with orientation, perception, concentration, memory encoding and retrieval, and judgment.

Further complicating recovery from mTBI is an assemblage of cognitive, physical, and emotional symptoms that can occur following mTBI, termed post-concussive syndrome (Bazarian, 2001; Lishmann, 1988; Vanderploeg 2007). Patients with post-concussive syndrome may complain of headaches, postural imbalance, insomnia, memory problems, fatigue, irritable or depressed mood, or interpersonal conflict (Lew, 2006; Vanderploeg, 2005). This syndrome is challenging to diagnose using a detailed physical exam or neuroimaging alone. It is often the case, unfortunately, that misattributions of underlying psychopathology prevent post-concussive syndrome patients from receiving appropriate care.

To date, studies which have attempted to detect the effects of mTBI in a population have produced only modest results. The natural course of concussion is to heal with few if any residual symptoms, (Wyman, 2008). Further, as also pointed out by Wyman, the current classification system for concussion is based upon the criteria of Kay and Associates (1993) which allows the diagnosis of mTBI with only a transient alteration of consciousness—easily non-neurologic in etiology—and thus the vast majority of mTBI subjects have suffered no unconsciousness nor loss of memory. If there is a common group neuropsychological correlate in such a population, it is likely transient and needs to be acutely measured in recent concussion.

Despite the prevalence of wartime mTBI, the chronological stages in improvement of related sequelae are poorly understood. Due to the complexity of injury, there has been a recent surge of research to improve techniques for early detection and assessment.

Clinicians and researchers have begun to recognize the utility of computerized testing for assessing neurological insult (i.e., mTBI; Register-Mihalik, Guskiewicz, Mann & Shields, 2007). There remains a paucity of evidence that computerized testing immediately following possible brain injury from blast exposure or alternative sources is beneficial. A study conducted by McCrea et al. 2005, reported increased sensitivity to acute concussion when comparing

neuropsychological testing to a brief battery consisting of a graded symptoms checklist (GSC), standardized assessment of concussion (SAC), and Balance Error Scoring System (BESS). The BESS has been studied for over 10 years (Broglio 2009) and has become a standard test for assessing concussion in high school and college athletes. They demonstrated the relative sensitivity of neurocognitive testing increased by five percent two days following concussion and by fourteen to thirty percent seven days following a concussion. They noted, however, that the increased sensitivity at seven days post-mTBI rate must be balanced against the false-positive rate of nine percent identified in the normal control group. A small but clinically significant percentage of injured athletes who reported being symptom free by day two continued to be classified as impaired on the basis of objective balance (the Balance Error Scoring System (BESS)) and computerized neurocognitive testing. These data suggest that neuropsychological testing may be of incremental utility to subjective symptom checklists in identifying the residual effects of sport-related concussion. The implementation of neuropsychological testing to detect subtle cognitive impairment is most useful once post concussive symptoms have resolved. This management model is also supported by practical and other methodological considerations (McCrea, 2008).

In the past, self reported symptom checklists were a significant tool used to evaluate sports-related concussions, but the lack of objective data made it difficult to properly assess those with concussions in the sports arena (Oliaro, 2001). The 2005 study by McCrea et al. indicated that objective balance was clinically significant even when there were no self-reported symptoms in a post-concussion group. The BESS is a modified version of the Romberg test and can be administered in less than 10 minutes. It is conducted under six stance conditions: a double-leg stance, single-leg stance, and heel-to-toe tandem stance – each on a firm surface, then on a flexible foam surface (Broglio, 2009). The subject is tested with their eyes open as well as eyes closed. During the trial, the number of errors an athlete makes is counted, with the higher number of errors representing suppressed balance. If there is an increase of three or more errors above the baseline this may represent a significant change indicative of a balance impairment (Valovish-McLeod, 2006) with a sensitivity to concussion reported at 34% and specificity at 91% (McCrea, 2005).

The BESS has been demonstrated to be both reliable and valid for sports-related concussions (Guskiewicz et al., 2001; Riemann et al., 1999; Riemann & Guskiewicz, 2000). The BESS is recommended for use with military personnel (Iverson, 2008). However, the BESS has often been noted as having poor inter-rater reliability. While the stances of the BESS are simple, often there is an issue with administrators' subjective evaluation of the test. One rater will count a fault while another rater watching the same subject would not. Thus this difference can result in a decrease in test reliability. Per Springer, Marin, Cyhan, Roberts, and Norman (2007), being able to remove the subjective portions of the test and reduce the number of stances conducted should result in a test with great reliability and validity. If the necessary clinical information can be gathered in a shorter period of time using two stances completed twice rather than three stances completed twice (on two different surfaces), that test may have greater clinical

application than the BESS when assessing for mTBI. The Unipedal Stance Test (UPST) is described as a method of quantifying static balance ability (Newton, 1989). In this test the subject stands barefoot, both on a hard surface and again of a foam surface, on the leg of their choice, with the other leg raised near, but not touching, the ankle of their supporting limb. The subject is asked to focus on a spot on the wall at eye level in front of them and to cross their arms over their chest. They are to hold this stance as long as possible or up to 45 seconds (Springer et al., 2007). The measure is then repeated with the patient's eyes closed. Each session is completed three times and is timed. The timing of the session is stopped if any of the following occur: the non-stance foot touches the floor, the arms are uncrossed, the stance foot shifts, participants open their eyes during the eyes closed test, or they reach the maximum time of 45 seconds.

Two computerized, neuropsychological tests, the Immediate Post-concussion Assessment and Cognitive Testing (ImPACT) and the Automated Neuropsychiatric Assessment Metric (ANAM) are currently being administered to active duty military personnel to assess for mTBI. However, there has been little research supporting the efficacy or accuracy of either test. Therefore, the best method for assessing mTBI has yet to be established. The most efficacious approach to addressing uncertainty surrounding the validity and clinical utility of the ImPACT and the ANAM is to systematically conduct research comparing the two tests, which will indicate the assessment that can offer the most accurate measurements of mTBI.

Currently there is a dearth of data in the scientific literature on the computer-based neurocognitive/neuropsychological test batteries and their use with active duty military personnel. According to Lovell (2001), the ImPACT 2.0 was designed to objectively measure visual and verbal memory, working memory, processing speed, visual motor skills, and reaction time to assist in the diagnosis and tracking recovery of the concussed individual. The test was developed at the University of Pittsburgh Medical School and has been widely used with high school and college athletes following sports related concussions. Lovell (2001) noted that the short administration time of 20 minutes as it relates to sports injuries relies on two administrations; one pre-season (baseline) and one post-injury, in order to measure cognitive deficits post-concussion. Research indicated one of the key attributes of the ImPACT was its ability to accurately identify cognitive data and post- concussive symptoms following an injury, as well as play a key role in determining whether the concussed individual is fit for play return to work, or requires additional evaluation or services. The military is currently using ImPACT MIL, which consists of ten cognitive tasks (subjective profile and health history questionnaire, current symptoms, injury description and conditions, and six neuropsychological tests (word discrimination, design memory, Xs and Os, symbol matching, color match, and three letters). The ImPACT MIL is currently being used to aid in the detection, diagnosis, and treatment of Special Forces soldiers with mTBI. It can be administered individually or in a group setting, thus making its administration to large groups easier than traditional paper and pencil neuropsychological tests.

In terms of sensitivity of specificity, Schatz et al. (2005) found that among high school athletes suffering from a concussion; the ImPACT was successful at identifying 85.5 % of the

cases as either concussed or non-concussed. Visual memory, reaction time, and processing speed subtest composite scores were found to be very sensitive to detecting mild concussion in high-school athletes. Sensitivity was reported at 81.9% and specificity at 89.4 %. A study by Van Kampen et al. (2006) supported the idea that objective neuropsychological tests may be more consistent than that of a measure of self-reported symptoms. According to Aubry et al. (2001), the risk of false negatives is higher when only paper and pencil neurocognitive measures are used due to the test's susceptibility to practice and learning effects.

ANAM is the culmination of a long line of computer-based test systems developed by the Department of Defense and evolved principally from the Unified Tri-Service Cognitive Performance Assessment Battery (UTC-PAB; Englund, Reeves, et al., 1987). According to Reeves et al. (2007), the ANAM was specifically designed to meet the needs of researchers and clinicians assessing neuropsychological function in long-term (6-12 months), short-term (daily to weekly), and within session repeated measures assessment. After the Center for the Study of Human Operator Performance (C-SHOP) based at the University of Oklahoma received the exclusive license for ANAM, researchers and staff at the center surveyed ANAM users, initiated a quality assurance assessment of the existing ANAM software, and then set about making improvements and innovations in order to produce an enhanced suite of ANAM software products that would provide greater uniformity, capability, and usability. C-SHOP released an improved version of the ANAM test modules (version 4.0 or ANAM4™) in the Fall of 2006. The ANAM4™ TBI MIL Battery is the current version being used by the military today. C-SHOP says the ANAM4™ TBI MIL Battery provides "precise, objective, automated measures of fundamental neurocognitive functions including response speed, attention/concentration, immediate and delayed memory, spatial processing, and decision processing speed and efficiency" (Helmick, et al., 2006). These qualities of the ANAM4™ TBI MIL Battery are consistent with past applications of computer-based testing of TBI, with normative work conducted by DVBIC, and with the Clinical Practice Guidelines and Recommendations published by the Defense and Veterans Brain Injury Center Working Group on the Acute Management of Mild Traumatic Brain Injury in Military Operational Settings (Helmick, et al, 2006).

Levinson and Reeves (1997) conducted a study in which a battery of ANAM tests was able to correctly classify brain-injured patients with 91% accuracy, a better level of accuracy than alternative neuropsychological tests or staff ratings. A review of recent studies involving ANAM by Cernich, et al. (2007) focused on the sensitivity and specificity of the ANAM. Bleiberg and Warden (2002) showed that none of the control subjects they tested showed a reliable decline on more than one ANAM test in comparison to all the injured subjects. Additionally, the Mathematical Processing test showed the greatest specificity for concussive injury. It was also noted by Bleiberg and Warden (2002) that the percentage of concussed subjects who failed to demonstrate practice effects was much greater in comparison to that of the control subjects.

Recently, portable, user-friendly EEG devices have been used in the detection and tracking of mTBI following sports-related concussions. The McCrea et al. 2010 study–using QEEG to track mTBI recovery in a cohort of 28 athletes–found QEEG results showed a typical course of recovery following concussion. However, the study also said QEEG findings "suggest that the duration of physiological recovery after concussion may take longer than observed clinical recovery." Naunheim et al. 2010 found the use of QEEG in a TBI-positive population to have 92.45% sensitivity and 90% specificity when compared to a CT for TBI, thus adding to the validity of QEEG as a sensitive index of brain function.

4.4.1 BrainScope QEEG Background Information

The BrainScope Ahead M-100 is a QEEG device indicated for use to aid in the triage of patients who are suspected of a traumatically induced structural brain injury and/or clinical maniffestions of functional brain injury, as a result of an insult to the head from an external force. BrainScope has spent many years and millions of dollars developing a medical device to address the unmet need for detecting the level of structural injury and functional impairment from TBI in an acute setting. The Ahead M-100 uses a sophisticated mathematical algorithms to collect and obtain an output that has clinical utility for the Military, Emergency Medicine and Sports Medicine. It has been specifically designed to accommodate current military environmental needs including digital signal processing and immunity to external noise interference.

The Ahead M-100 device is a single-use, proprietary headset containing pre-gelled electrodes will be placed on the subject's forehead and earlobes according to the standard locations of the modified International 10/20 system, including: FP1, FP2, AFZ, F7, F8, left and right earlobes and a ground at FPZ. The forehead will be cleaned with a mild abrasive sponge used as standard practice to improve contact of the headset with the skin. All electrode impedances will be below 10kΩ prior to the start of the recording.

Subjects will undergo approximately 5 minutes of eyes closed EEG recording. At the end of 5 minutes, if the device has acquired 48 epochs (each 2.5 seconds) of artifact-free data, the embedded algorithms will process the stored data to obtain the classification result. If 48 epochs were not recorded in 5 minutes, the device will continue recording for an additional 5 minutes. In no instance will the algorithm use fewer than 24 epochs of artifact-free data to calculate the BrainScope Classification Output.

The Ahead M-100 utilizes a combination of three classification algorithms that enable discrimination among 4 patient groups. These classification algorithms are combined in a sequential fashion that maximizes accuracy (sensitivity and specificity) of classification.
The sequence of the classifiers to determine the Ahead M-100 Classification in which a patient belongs is as follows: [1] The first classifier discriminates between patients in Group 4 and all other Groups combined (all "non-4"). For a patient identified as a "4", the classification process is over and the results are displayed; if not classified as a 4, then [2] a second classifier is used to discriminate patients in Group1 from the balance of the patients (2, 3, or 4). For a patient

identified as a "1", the classification process is complete; if not classified as a "1", then [3] a third classifier is used to discriminate patients in Groups "2" and "3". This sequence separates the patients into the 4 classifications uniquely.

Potential Physician Interpretation of Device Output

Device Output	Potential Output Interpretation	Potential Physician Interpretation
4	• Structural brain injury (positive CT finding)	• Obtain a head CT rapidly • Transfer to higher level of care if CT is unavailable.
3	• Non-structural brain injury and more severe clinical manifestations of functional injury	• Do not release the patient • May require further evaluation • Hold for close, medical observation • Clinician may decide to obtain CT based on other assessment factors (History of event, LOC, PTA, symptoms, etc.)
2	• Non-structural brain injury and less severe clinical manifestations of functional injury	• Patient may be released if consistent with other assessments (neurological exam, symptoms, etc). Re-evaluation should be scheduled.
1	• Normal or patients without head injuries	• Normal patient, may be released if other assessments are normal. • Re-evaluation only for new or exacerbated symptoms.

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4.6 Research Design and Methods:

SUMMARY:

The study consists of two arms. Each arm will be given the same set of automated neurocognitive test batteries. The participants will be as follows: 100 cases of acute concussion, which will be tested using the ANAM4™ TBI MIL, ImPACT MIL, AHEAD M-100 and the

UPST. A sample of 200 normal healthy soldiers will be given the ANAM4™ TBI MIL, ImPACT MIL, AHEAD M - 100 and UPST. Controls are necessary to establish the use of the ANAM4™ TBI MIL and the ImPACT MIL on normal healthy active duty military controls. The order in which the tests are administered will be changed so that half of the concussed and control group participants take the ANAM4™ TBI MIL first and then the ImPACT MIL while the other half will take the ImPACT MIL first and then the ANAM4™ TBI MIL, thus allowing for a counterbalance of any possible order effect, carryover, or fatigue. The effects of carryover or fatigue is unknown at this time. The test manufactures believe it would be minimal, however, this is an important variable to determine. Between the two test administrations participants will be given a brief break before beginning their second test battery. At some point during test administration a short EEG, known as AHEAD M - 100, will be given. The AHEAD M-100 device is a handheld portable EEG (brain electrical signals) monitor. The monitor involves the use of a non-invasive adhesive headset to collect the data in a very similar way to the ECG monitor for the heart. The device performs some initial processing of the EEG signal giving each patient a score from one to four which reflects their clinical risk. Study personnel will be blinded to the clinical data. The results of testing will not be shared with the clinicians involved in treatment decisions to be assured that treatment plans are not influenced. For purposes of the study, the BrainScope Classification result will not display at the conclusion of the test. The result will be stored on the device and electronically transferred to the study monitor for data analysis. This data will be used for study analysis, but not for clinical decision-making. During the break period the UPST will be administered and scored. All tests will be administered by staff trained in the administration of the ANAM4 TBI MIL, ImPACT MIL, UPST, and AHEAD M - 100.

SAMPLE SIZE:

This study will use a target sample size of 100 acutely concussed cases and 200 active duty military controls, for a total study size of 300 participants with full data sets. The large sample size will provide sufficient power of .90 to detect between and with in-group effects.

RECRUITMENT/ELIGIBILITY:

Participants in the concussion group will be recruited from the Emergency Department (ED) at each of the research locations: (SAMMC), (CRDAMC), (LRMC), , (MACH) and (TAMC), each site will define testing locations as necessary. All participants will be age 18 – 55. All research investigators will work at the hospitals in question and will have appropriate staff identification and access. Participants with a diagnosis of mTBI will be contacted and tested within 72 hours of the concussion event. Participants may be recruited from the ED and tested on site or may have an appointment scheduled for testing within 72 hours post-concussion.

Recruitment from the ED will include participation from the ED staff to aid in identifying those with possible concussion. The ED staff will be informed about the study and referral information will be given to the staff. Also a member of the study team will be placed in the ED

and will recruit from there when appropriate for them to do so without interrupting the ongoing functions of the ED. If a member of the study team is not at the ED at time of discharge the concussed person will be given the research assistances contact information and asked to contact them as soon as possible pertaining to the study. No patient HIPAA information will provided to the research staff by the ED staff. The ED staff will act to identify possible participants and initial study contact will be made either using a study recruitment flyer or by study staff located in the ED at the time.

Study recruitment for controls will be conducted at the SRP site in a group setting prior to the administration of the ANAM. Service members are tested in groups of 25 – 50 depending on the size of the testing location. Prior to testing, testing instructions are given to group members in a class like setting. Recruitment of potential control group members will be conducted at that time. Recruitment efforts will be brief consisting of a non-military civilian research assistant giving a brief (less than 5 minutes) speech to the group asking for participants (see appendix). Participants who choose to participate in the study will be asked to move into a separate designated testing area to continue with the consent, screening questionnaire and testing.

INCLUSION CRITERIA:

1) TBI-positive group [mTBI]. Individuals age 18 – 55 who have access to care at the medical treatment facilities used in the gathering of research, who report to a level II point of care for suspected concussion/mTBI, and who subsequently meet the DoD criteria for acute concussion as determined by gathered information set forth on page 1 of the MACE which has been incorporated into the screening questionnaire used for this study. Participants must be fluent in English.
2) Healthy military control group [HMC; no-TBI]. Military controls will consist of otherwise healthy soldiers, 18 – 55 years of age, and recruited from the Soldier Readiness Processing (SRP) site at Ft. Hood, Texas, and Schofield Barracks, Hawaii. These soldiers will be asked to participate in the study since they are already scheduled to take the ANAM4 TBI MIL as part of the SRP requirements. Participants must be fluent in English.

EXCLUSION CRITERIA:

1) TBI-positive group [mTBI]. Individuals taking any mind-altering medication or reporting a level of pain >7 (10 point scale). If the Principal Investigator determines that individuals with lower pain levels are unable to focus attention adequately on the neurocognitive assessment task, the exclusion criteria will be expanded with approval of the IRB. Individuals with disorders requiring any of the following medications will be excluded from the study, any anti-psychotic medications or Phenothiazane (e.g. Seroquel, Thorazine, Haldol, or Olanzapine). Anyone taking any kind of Benzodiazepines (e.g. Valium or Klonopin) will be excluded. Other exclusionary medication will include Benadryl or similar sedating antihistamines, stimulants such as Ritalin or other

Amphetamines and mood stabilizers (e.g. Tegretol, Lithium, Topamax, Depakote, or Lamictal). Individuals who report the use of any mind altering substances within eight hours prior to testing will be excluded from participating. Female participants who are pregnant will also be excluded from the study.

2) Healthy military control group [HMC; no-TBI]. Individuals will be excluded from participation if they have a history of mild traumatic brain injury within 90 days, moderate brain injury within the past three years, or any lifetime history of severe brain injury. Individuals who are on any mind altering medication or report a level of pain >7 (10 point scale). If the Principal Investigator determines that individuals with lower pain levels are unable to focus attention adequately on the neurocognitive assessment task, the exclusion criteria will be expanded with approval of the IRB. Individuals who report the use of any mind altering substances within eight hours prior to testing will be excluded as will pregnant females. Use of certain medications will also result in exclusion from the study, including: any anti-psychotic medications or Phenothiazane (e.g. Seroquel, Thorazine, Haldol, or Olanzapine), Benzodiazepines (e.g. Valium or Klonopin), Benadryl or similar sedating antihistamines, stimulants such as Ritalin or other Amphetamines, and mood stabilizers (e.g. Tegretol, Lithium, Topamax, Depakote, or Lamictal).

PROCEDURE:

1) TBI-positive group. Participants in the concussed group will be tested individually. They will either be tested at the Emergency Department (ED) or at an office near the ED following their discharge from the ED. Or if admitted for observation or other health issues, testing may be conducted in the participant's room at the hospital. If, for any reason, the participant is either unable to test at that time or does not feel comfortable testing in the ED, an appointment for testing within the 72 hour window after the concussion can be made. If testing cannot be completed within the 72 hour post-concussion window, the participant will be excluded from the study. Because the concussed subjects will be recruited from four different research sites, the order in which the tests are administered will be alternated for each participant at each location. Informed consent will be obtained prior to testing and participants will be given the opportunity to ask questions both before and after testing. Before any testing begins the completion of a screening questionnaire will be required and completed by the research staff in order to ensure the participant meets study criteria. Contact information for follow-up research and delivery of testing results is included within the informed consent. Participants will be contacted by phone one week (7 days) post-concussion and will be asked about their current post-concussion symptoms. This will include questions from page one of the screening questionnaire and should be less than 5 minutes in duration.

2) Both the ANAM4 TBI MIL and ImPACT MIL will be administered in accordance with the current guidelines used for administration by the military. The estimated testing time is approximately 60 minutes. The test battery will include the screening questionnaire (see appendix), which incorporates the same information as the first page of the Military

Acute Concussion Evaluation (MACE), currently used to identify mTBI per DoD standards; the ANAM4 TBI MIL instructions and testing (25 minutes); the UPST instructions and testing (5 minutes); the ImPACT MIL instructions and testing (20 minutes) ; and the AHEAD M - 100 (10 minutes) will comprise the test battery for this study.

3) Healthy military control group. Participants in the control group will be active duty soldiers recruited from the Soldier Readiness Process (SRP) sites at Ft. Hood and Schofield Barracks. As part of their SRP soldiers are required to take the ANAM4™ TBI MIL. As per military standards the ANAM4™ TBI MIL will be administered in a group setting. Given that the soldiers are already taking one of the two tests being compared, they will be asked to volunteer to take the ImPACT MIL, AHEAD – M 100 and UPST, which will add roughly 40 minutes to their overall testing time. For those who choose to participate they will complete the screening questionnaire in order to ensure those being tested meet the study criteria for inclusion and then the first 100 participants will take the tests in the following order: ANAM4 TBI MIL + ImPACT MIL and the next 100 vice versa. Between each test administration a short break will be given. Before starting the second test the UPST will be administered and scored. The administration of AHEAD M - 100 will occur either before testing begins or following test completion. The order of test administration will be tracked by the test administrator on the questionnaire form provided in appendix A.

Time frame:

Data collection is expected to last 330 days from the start of the study once it is approved by the IRB.

Test results reporting:

Testing results will be reviewed by the PI with disposition to follow. Reports will be mailed out to participants if testing indicates any abnormalities. Participants may choose to include these reports as part of their medical records. The reports may also be used by medical care providers and may help in determining diagnosis and course of treatment for participants.

4.7 Number of Subjects:

TOTAL NUMBER OF SUBJECTS (nation-wide/study-wide) 300

Subjects will be recruited until the number of concussed (mTBI) participants reaches 100 and the number of military control subjects reaches 200. The following power analysis was based on Aim #1 for the ANOVA model. Given the desire to maintain a 2:1 ratio of control to mTBI participants, a power analysis was performed given the following parameters: level of significance of .05, power of .8, a conservative 2-sided test, and a medium effect size: Cohen's d = .5 (standardized effect size). Using the harmonic mean for deriving sample size (based on the desired 2:1 ratio) as found in Cohen (1988): $n' = 2nA\,nB/(nA + nB)$ a power of .81 for a medium

effect size is achieved when 100 controls and 50 experimental subjects (n' = 66.67) are sampled; thus, a total sample size of N = 150 will suffice if a medium effect size is attained. Initially it was proposed that 200 controls and 100 experimental subjects would be sampled (N = 300); if this was to be the case, a power of .98 (n' = 133.33) would be obtained. Note that an approximate power of .8 for 200 control and 100 experimental subjects will be obtained if the effect size is .35 (which is a more conservative, albeit safer, effect size estimate).

5.0 Human Subject Protection

5.1 Source of Data:

No additional data sources will be used at this time for this protocol.

5.2 Benefits:

This is an important study. The study will help to ensure the clinical instruments that are currently being used to detect mTBI in the active duty army population are actually measuring what needs to be measured. This will make it possible to diagnose mTBI faster and more accurately, increasing the Army's ability to monitor the Soldier's status, recovery, and return-to-duty potential.

Benefits to concussed subjects participating in the study will include optional documentation of their neurocognitive functioning within 72 hours of their concussion. Subjects can retain the documentation for their medical records.

There is no direct benefit to those in the control group for their participation.

5.3 Risks:

The PI of this protocol will use a continuous monitoring process to insure the data at participating sites is of high quality and the study is properly conducted.

- Pre-Training: Each site will be visited by a training team comprised of PI verified experts on the tools and techniques of the study and train study personnel to criteria on proper data collection for the study prior to any data being collected.
- The local PI will, in all cases, be a licensed and credentialed independent health care provider known to be of good character and in good standing with their health care facility.
- The PI will visit each site early in the data collection process to insure proper procedures are being followed.
- All subject data will be returned to the primary coordinating center as collected, where they will be audited to insure that:
    - Informed consent is properly signed
    - Informed consent is properly witnessed
    - All demographic information is properly completed
    - All study information is properly collected and coded.
    - If any record appears to have any irregularities, the subject will be contacted by the PI to insure they were properly consented, and the data was properly collected.

Foreseeable Risks. Neuropsychological testing by its nature is non-invasive and involves no risk of physical harm for any participant. Since these are cognitively taxing exercises, however, individuals may become frustrated or unhappy if they are performing poorly. Examiners are trained in reassurance and encouragement to obtain the patient's best performance.

The BrainScope AHEAD M-100 is a non-invasive, "non-significant risk" (NSR) device per FDA guidance entitled, "Significant Risk and Non-significant Risk Medical Device studies". A letter from BrainScope Company, Inc. is attached as appendix E to this protocol. In order to fully comply with the abbreviated IDE requirements for the AHEAD M-100, the following requirements have been met:

- The device is labled in accordance with the labeling provisions of the IDE regulation 812.5 – "CAUTION – Investigational Device. Limited by Federal law to investigational use."

- Study PI will obtain and maintain IRB approval throughout the investigation as non-significant risk device study.
- Informed consent will be obtained from each participant in accordance to 21 CFR 50.
- Proper monitoring of the application and data collection of this device and compliance under the approved protocol will be maintained by AI's and research staff.
- Records and reports will be maintained as indicated in section 5.4 of this protocol
- At no time during this study will the AHEAD M-100 be commercialized, promoted, test marketed, misrepresented as anything other than an investigational device by the study AI, PIs or research staff.

It is recognized that the QEEG evaluation is noninvasive and uses passive sensors, so that no electrical current is put into the brain. In order to obtain good sensor connections, it is not unusual for the skin to require cleaning to remove oilss and dead skin cells. A cleansing sponge provided by the manufacturer will be used for this purpose. This may result in the risk of mild skin irritation (temporty reddening of the skin lasting only a few minutes) for some participants in tiny areas under the sensors creating the only foreseeable risk. The most significant foreseeable adverse outcome to the patient would result from triggering the Reporting Criteria mandated by UCMJ. The informed consent process makes clear, and this will be verbally instructed as well, that "there are limits to confidentiality in health care information, and we will be mandated to report serious crimes, such as war crimes, danger to self or others, or domestic abuse."

Risk Management and Emergency Response. If the research participant becomes frustrated, they will be allowed to rest until they regain composure and feel they are able to give their best performance. If the research participant is deemed a danger to him or herself or others, appropriate emergency medical systems will be employed. All research will take place in a Health Care Facility of at least level II, and any medical crisis or emergency will engage this health care systems' response.

Measurements taken to Minimize Risk. Testing will be paced with a programmed break period each hour. All testing will be done in a climate-controlled area, and participants will be allowed to get water between testing sets. Subjects can terminate testing at any time.

Adverse Events

Consideration of Adverse Events will hereafter consist of Adverse Events and Adverse Device Effects, including anticipated adverse device effects and unanticipated adverse device effects.

<u>Adverse Event:</u>
Any untoward/undesirable clinical occurrence in a clinical investigation of a Subject using a device and/or product and which does not necessarily have a causal relationship with this

treatment. An Adverse Event can therefore be any unfavorable and/or unintended sign, symptom, or disease temporarily associated with the use of a device or product, whether or not it is considered related to the device product.

Anticipated Adverse Procedure Effect:
Any adverse effect related to the procedure (QEEG), which is identified in the protocol prior to study commencement.

Unanticipated Adverse Procedure Effects:
Any adverse effects on health or safety or any life threatening problem or death caused by, or associated with, a procedure, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the protocol or application (including a supplementary plan or application) or any other unanticipated problem associated with a procedure that relates to the rights, safety or welfare of Subjects (see Appendix F - Reportable Event Submission Form - IRBO). All Adverse Events occurring during the study procedure (venipuncture) and immediately after (within 30 minutes), whether or not attributed to the venipuncture, observed by the PI/AI or reported by the Subject, will be recorded on the Adverse Event CRF.

Safety Monitoring
The PI/AIs will monitor all Adverse Event reports to identify and trend all events that would require temporary discontinuation of study enrollment, to fully characterize device safety, to modify the study protocol, or to terminate the study.

Reporting Procedures for All Adverse Events
After review with the Subject by the study PI/AIs, all Adverse Events will be documented in the Subject's source document and on the appropriate Reportable Event Submission Form. The following attributes must be assigned:

- description of event
- date of onset
- date of resolution
- duration
- severity
- relationship to the study procedures
- actions taken
- outcomes
- attending physician treating event
- determination as to whether event is anticipated or unanticipated

If the Adverse Event is of such severity in the Investigator's judgment that it warrants withdrawal from the study, the Subject should be withdrawn and a termination assessment

performed (EOS CRFs completed). The Subject should be given appropriate care under medical supervision until symptoms resolve.

Adverse Events are described as mild, moderate or severe. The severity of Adverse Events will be assessed on the following severity index scale:

- Mild - The Adverse Event is transient, requires no treatment, and does not interfere with the study Subject's daily activity.
- Moderate - The Adverse Event introduces a low level of inconvenience or concern to the Subject and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.
- Severe - The Adverse Event interrupts the Subject's usual daily activity and requires systematic therapy or other treatment. Severe is defined as a measure of the intensity of a reaction, effect, or experience.

The relationship of an Adverse Event to the study will be graded as follows:

- None - The Adverse Event is not associated with the study device use.
- Remote - The temporal association is such that the study device is not likely to have had an association with the observed Adverse Event.
- Possible - This causal relationship is assigned when the Adverse Event:
  - Follows a reasonable temporal sequence from device use, but
  - Could have been produced by the study Subject's clinical state or other modes of therapy administered to the study Subject.
- Probable - This causal relationship is assigned when the Adverse Event:
  - Follows a reasonable temporal sequence from device use,
  - Abates upon discontinuation of the treatment.
  - Cannot be reasonably explained by known characteristics of the Subject's clinical state.
- Highly Probable - This causal relationship is assigned when the Adverse Event:
  - Follows a reasonable temporal sequence from device use,
  - Abates upon discontinuation of the treatment, and
  - Is confirmed by the reappearance of the Adverse Event on repeat exposure.

All unanticipated problems involving risk to subjects or others, serious adverse events related to participating in the study, and subject deaths related to participation in the study should be promptly reported by phone (b)(6) by email (b)(6) or by facsimile (b)(6) to the USAMRMC Office of Research Protections, Human Research Protection Office (HRPO). A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

Reports will be submitted to the BAMC IRB as well as the local IRB if occurring at different study collection point if the Adverse Events are related to the study design or procedures.

Serious and Expected Adverse Events. Reportable Event Submission Forms (Appendix G) will be submitted to the HRPO with the Continuing Review.

Deaths

Deaths which must be reported to the Human Research Protection Office/Institutional Review Boards include:

- All deaths while participating in the study.

For all deaths, copies of available autopsy reports and relevant medical reports should be sent to the sponsor or its designee with Subject's name masked (except for the first initials of the first and last name).

Withdrawals for Adverse Events

All Adverse Events which result in the Subject's withdrawal from the study must be reported immediately by telephone or e-mail to USAMRMC.The Investigator may be asked to provide detailed follow-up information. The PI/AI will report to the appropriate regulatory authorities. The PI/AIs must notify their own IRB of all Unanticipated Adverse Device Effects occurring at the site, and Unanticipated Adverse Events reports.

Protocol Deviations

Protocol deviations or violations that have occurred, have not been pre-approved by the HRPO, and which may adversely affect the rights, safety, or welfare of subjects, or the integrity of the research data will be recorded immediately on discovery by the PI/AIs. Unanticipated protocol problems will also be reported in this way, and include problems that pose a risk to subjects, affect others in the research study, or which significantly impact the integrity of the research data, such as breaches in confidentiality and losses or destruction of research or study samples.

Any deviation from the protocol that may have an effect on the safety or rights of the Subject or the integrity of the study must be reported to the USAMRMC ORP HRPS as soon as the deviation is indentified.

Reporting Unanticipated Problems Involving Risks To Subjects Or Others, Serious Adverse Events And Deaths To The HQ, USAMRMC IRB.

All unanticipated problems involving risk to Subjects or others, serious adverse events, and all Subject deaths will be promptly reported by phone (b)(6) by e-mail (b)(6) by facsimile (b)(6) to the HQ, USAMRMC IRB, or sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RP, 504

Scott Street, Fort Detrick, Maryland 21702-5012. A complete written report will follow the initial notification.

5.4 Safeguards for Protecting Information:

All of the data will be identified with a study participant number rather than the participant's name to maintain confidentiality. The master list will be maintained by the PI during the course of the study. All electronic data will be stored on a secure, password-protected computer. No computer used for storing data will be connected to the server at any time. All paper research records will be kept in a locked file prior to being transferred to a locked file and office at the Warrior Resiliency Program (WRP) BAMC. All electronic research records will be kept in a password-protected computer in the investigator's designated locked office at WRP. As the primary center for this study the staff at BAMC will be the collection point for all participating data collection sites. The electronic information will be sent to the staff located at the WRP, Lincoln Center location weekly for data processing and storage. Each site will save encrypted (Credent To Go) testing data to a CD and then upload that data to a limited access Army Knowledge Online folder for retrieval. After the information has been uploaded from the CD the CD will be destroyed.This information will be retained at WRP during the life of the protocol. Data confidentiality will be strictly protected. Only individuals immediately involved in the study will have access to files that include subject identifying information. The only exceptions to Confidentiality would be for legally mandated disclosures as verified by BAMC's Judge Advocate General, or modification to this protocol approved by the BAMC IRB. Group data will be summarized in final report documents, and aspects of individual volunteer's performance may be reported as well; however, participants' names will never be published as a contributor of specific data points or as a participant in the investigation.

The data will be archived and may be used or included in subsequent studies for purposes which cannot be anticipated at the present time. All guarantees of anonymity and confidentiality will still apply.

When the results of the study are printed or talked about in conferences, no information will be given out that would tell anyone whom the participants are. Records of participants taking part in this study may only be made public in accordance with federal law, including the Federal Privacy Act, 5 U.S.C. 552a, and its implementing regulations. DD Form 2005, Privacy Act Statement-Health Care Records, contains the Privacy Act Statement for the records. If participants sign this consent form, they give their permission for information that we get from their participation in this study to be printed in medical literature, discussed for teaching purposes, and used to further medical science. All information about participants will be given without identifying them.

5.5 Informed Consent:

Informed consent will be collected prior to collection of data or testing. Each testing site will have either an Associate Investigator or research assistant on the protocol with appropriate CV and CITI training available to answer any questions regarding the study and who will be responsible for ensuring informed consent is appropriately obtained and properly recorded. The Informed Consent forms are different for the Concussion and Control groups they are attached in the appendices.

Because this study is limited to individuals with mTBI only, it is not anticipated that the mental capacity of any volunteer will be severely compromised. If, however, an individual does not appear capable of giving informed consent for whatever reason they will not be included in the study. Mind-altering substances such as tranquilizers, conscious sedation, or anesthesia are exclusion criteria, and service members using those will not be allowed to participate. All subjects will be 18 – 55 years of age. Individuals will not be rushed into making the decision to participate and will be allowed to discuss any concerns in private.

6.0 Data Analysis:

Study Aims/Endpoints:

This exploratory study will examine the sensitivity and specificity of three novel devices which are hypothesized to be useful in the diagnosis of concussion (mTBI). Patients with a known concussion (mTBI) meeting the DoD definition of concussion will be compared to matched soldiers with no recent concussion history. Each instrument provides a graded output: Normal/mild/severely abnormal. A multivariate approach will initially be pursued, incorporating all of the instruments simultaneously in the predictive model. This global approach will aid in ascertaining accuracy of classification between groups for each instrument, and as well take into account the extent of collinearity between the instruments.

To test the given the dichotomous outcome (i.e., mTBI vs. control) a multiple binary logistic regression will be conducted. A logistic regression and may also incorporate the key predictors (e.g., QEEG) to determine not only the predictive power of each predictor (e.g., logit, odds ratio, etc.) but to also extract classification information on sensitivity (true positives) and specificity (true negative). The results of this analysis can also be used to conduct a receiver operating characteristic (ROC) analysis and a significance test for area under the curve (AUC). There are various ways by which to assess model fit in logistic regression (Hosmer & Lemeshow, 1989), those being as follows:

1) A chi-square test is conducted to see if the model is improved when the predictor are entered. If significance is obtained ($\alpha = .05$) then the addition of the covariates indicates

model improvement over and beyond the origin only model (the difference in -2LL are used for the test statistic).

2) The Hosmer-Lemeshow goodness-of-fit test is used to ascertain how well the model fits the data. For this test, a non-significant result is desired.

3) The individual logits (log of the odds) will be examined and tested for each predictor. Again, a level of significance of .05 will be the nominal level of significance for each covariate. Moreover, the odds ratio (OR) and the accompanying 95% confidence interval (CI) will be furnished for each variable. If the CI around the OR does not include 1.0, then significance is obtained.

4) Additionally, sensitivity (hit rate for true positives) and specificity (hit rate for true negatives) will also be computed for each of the logistic models; hence affording the opportunity to draw comparisons between the instruments (i.e., ANAM, IMPACT).

Any other variables germane to the test of the model, such as UPST and/or EEG will also be incorporated if deemed warranted. Moreover, in a reversal of the model, it may be of interest to conduct a multivariate analysis of variance (MANOVA) to see if the two treatment arms differ on the linear combination of the instruments.

The role of post hoc analysis: it may be reasonably argued that membership in the category "normal control" does not guarantee lack of pathology in this group. All control members will fill out a TBI history questionnaire and symptom checklist. this data may be reanalyzed to factor in past history of TBI and whether abnormal controls are truly a 'miss'.

Further, it is possible members of the concussed group may have recovered from their concussion prior to testing. Participants will be evaluated based on the number of current symptoms for evidence of recovery.

As a further extension for analyzing sensitivity and specificity (1 - specificity will be on the x-axis), a Receiver Operating Characteristic (ROC) graphic will be furnished for each of the instruments shedding insight into the relationship of true and false positives. Moreover, another function of the ROC analysis is the possibility of locating area under the curve (AUC) so as to detect optimal cut points.

Additionally, though not a specific aim, so as to assess the extent of convergent validity (i.e., instruments measuring similar constructs should exhibit substantive correlations) a bivariate correlation will be computed for each of the instruments. Though there is no rigid cut-point as to what constitutes convergent validity (AERA, 1999), it is anticipated that correlations will be at least > .3 (i.e., 9% shared variance) which approximates a medium effect size per Cohen (1988) and will then provide preliminary evidence of convergent validity. Another exploratory approach that can be used to shed insight into classification, is finite mixture modeling. Akin to cluster analysis, in this case the group is an unknown quantity, but based on the model covariates (e.g.,

ANAM, IMPACT, QEEG, certain demographics or ancillary test scores) and their inter-correlation, classification based on maximizing homogeneity within groups and heterogeneity between groups can be exploited (McLachlan & Peel, 2000) and thus engender a closer examination of characteristics unique to these unknown classes.

References

AERA, APA, NCME (1999). Standards for Educational and Psychological Testing. DC: AERA. (Standards)

Cohen (1988). *Statistical power analysis for the behavioral sciences.* (2nd Ed.). Hillsdale, NJ: Lawrence Erlbaum.

Hosmer, D. W., & Lemeshow, S. (1989). *Applied logistic regression.* NY: John Wiley.

McLachlan, G., & Peel, D. (2000). *Finite mixture models.* NY: John Wiley.

7.0 Duration of Study:

Estimated start date and approximate duration of the study:

The study is expected to start in May 2011 data collection is expected to take no longer than four months (120 days) and analysis of data to take an additional six months (180 days) after data collection is complete for a total research time of 10 months (300 days).

8.0 Funding:

Support for materials and supplies will be provided by Medical Research and Materiel Command through a congressionally mandated research grant. Additional manpower for data collection will be obtained through the Grant Administrator at The Geneva Foundation.

9.0 Signature Section:

9.1 Principal Investigator:
I am aware that I am not authorized to accept any funds or other form of compensation for conducting research. All subjects will be treated in compliance with all applicable organizational, service, DoD and Federal regulations, and all applicable FDA and HHS guidelines.

_____ Date _____

(b)(6) Ph.D., (Clinical Neuropsychologist)
(b)(6)

9.2 Associate Investigator Signature Page

I have read the above protocol and agree with its content. All subjects will be treated in compliance with all applicable organizational, service, DoD and Federal regulations, and all applicable FDA and HHS guidelines.

_____ Date _____

(b)(6) Ph.D., ABPP (Clinical Neuropsychologist)
(b)(6)

I have read the above protocol and agree with its content. All subjects will be treated in compliance with all applicable organizational, service, DoD and Federal regulations, and all applicable FDA and HHS guidelines.

_____ Date _____

(b)(6) Ph.D.(Clinical Neuropsychologist/Medical Psychologist)
(b)(6)

I have read the above protocol and agree with its content. All subjects will be treated in compliance with all applicable organizational, service, DoD and Federal regulations, and all applicable FDA and HHS guidelines.

_____ Date _____

(b)(6) PT, DPT, OCS,(Physical Therapist)
(b)(6)

I have read the above protocol and agree with its content. All subjects will be treated in compliance with all applicable organizational, service, DoD and Federal regulations, and all applicable FDA and HHS guidelines.

_____ Date _____

(b)(6) Ph.D., MAJ (Clinical Neuropsychologist)
(b)(6)

I have read the above protocol and agree with its content. All subjects will be treated in compliance with all applicable organizational, service, DoD and Federal regulations, and all applicable FDA and HHS guidelines.

_____ Date _____

(b)(6) Psy.D. (Clinical Neuropsychologist)
(b)(6)

I have read the above protocol and agree with its content. All subjects will be treated in compliance with all applicable organizational, service, DoD and Federal regulations, and all applicable FDA and HHS guidelines.

_____ Date _____

(b)(6) Ph.D. (Clinical Neuropsychologist)
(b)(6)

I have read the above protocol and agree with its content. All subjects will be treated in compliance with all applicable organizational, service, DoD and Federal regulations, and all applicable FDA and HHS guidelines.

_____ Date _____

(b)(6) MD, MSM, FACEP
Colonel, Medical Corps, US Army
(b)(6)

I have read the above protocol and agree with its content. All subjects will be treated in compliance with all applicable organizational, service, DoD and Federal regulations, and all applicable FDA and HHS guidelines.

_____ Date _____

(b)(6) – (Clinical Psychologist)
CPT, MS
(b)(6)

I have read the above protocol and agree with its content. All subjects will be treated in compliance with all applicable organizational, service, DoD and Federal regulations, and all applicable FDA and HHS guidelines.

_____ Date _____

(b)(6) (Rehabilitation Psychologist)
(b)(6)

9.3 PI Service Chief (BAMC)

I have considered this protocol and am able to approve personnel and resource support. I understand that I will be the point of contact for correction of deficiencies should the principal investigator fail to meet the requirements agreed to in the Letter of Compliance.

_____ Date _____

(b)(6) Psy.D.
COL, MS
(b)(6)

9.4 Statistical Review

I have reviewed the data analysis plan for this protocol and approve of the plan as written. I understand that I will be the point of contact for this project's data analysis.

_____ Date_____

(b)(6) Ph.D.
(b)(6)

9.5 Scientific Merit Review:

This protocol has been reviewed and found to have sufficient scientific merit for consideration by the Institutional Review Board.

_____ Date_____

(b)(6)

Lt Col, USAF, MC

(b)(6)

Appendix A – Questionnaire

Demographic Information

Gender: ☐ Male ☐ Female

Date of Birth: _____(month/day/year) Age: _____

Ethnicity: _____

Marital Status: ☐ Single ☐ Married ☐ Separated ☐ Divorced ☐ Widowed

Education: ☐ No HS Diploma ☐ HS Diploma ☐ College Courses
☐ College Degree ☐ Graduate Degree ☐ Professional Degree

Total Education in Years: _____

Military:	Civilian:
Branch of Service	Occupation
Rank/Grade	Prior Military Service ☐ Yes ☐ No
Time in Service	Military Dependent ☐ Yes ☐ No
MOS	
Deployed OEF/OIF	
Number of Deployments	

Rate your current level of pain **TODAY** -From 1 (nothing) to 10 (The worst pain you can imagine):

None 1 2 3 4 5 6 7 8 9 10 Severe

How would you rate your **OVERALL** physical health?

Poor 1 2 3 4 5 Excellent

How would you rate your **OVERALL** mental/emotional health?

Poor 1 2 3 4 5 Excellent

History of Health Problems and Treatment:

Are you on any current prescribed medication? ☐ Yes ☐ No

Type/Dosage:

a.

b.

c.

d.

List any non-prescription medication, supplemental vitamins or alternative medications (ex. St John's Wort, Kava, Melatonin, Glucosamine)

a.

b.

c.

d.

Have you been diagnosed with a concussion in the past? ☐ Yes ☐ No

If yes, when? _____

How many concussions have you had? ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 or more

Height: _____inches Weight: _____lbs.

Have you ☐ lost ☐ gained weight in the past 3 months? _____lbs.

How many hours of sleep do you get per night? _____

Any ☐ increased ☐ decreased sleep in the past 3 months? _____hours

Do you have problems falling asleep, restless sleep, early awakening? ☐ Yes ☐ No

How much sleep did you get in the last 24 hours? _____ hours

Do you drink alcohol? ☐ Yes ☐ No

Have you had any alcohol in the last 8 hours? ☐ Yes ☐ No

Have you taken any mind altering substances in the last 8 hours? ☐ Yes ☐ No

If yes, what did you take? _____

Have you ever been diagnosed with a learning disorder? ☐ Yes ☐ No

Have you ever had brain surgery of any kind? ☐ Yes ☐ No

Do you have a seizure disorder? ☐ Yes ☐ No

The following is to be completed by study staff: Post Concussion Group ONLY

Description of Incident:
What happened?

Tell me what you remember?

Were you dazed, confused, "saw stars" ☐ Yes ☐ No

Did you hit your head? ☐ Yes ☐ No

Cause of Injury? (Circle all that apply):

- ☐ Motor vehicle accident
- ☐ Fall
- ☐ Sports related
- ☐ Other _____

Was a helmet worn? ☐ Yes ☐ No

Amnesia before: Are there any events just BEFORE the injury that are not remembered? (Assess for continuous memory prior to injury)

☐ Yes ☐ No If yes, how long _____

Amnesia after: Are there any events just AFTER the injuries that are not remembered? (Assess time until continuous memory after the injury)

☐ Yes ☐ No If yes, how long _____

Does the individual report "blacking out" or loss of consciousness?

☐ Yes ☐ No If yes, how long _____

Did anyone observe a period of loss of consciousness or unresponsiveness?

☐ Yes ☐ No If yes, how long _____

Have you had any concussions in the last 12 months?

☐ Yes ☐ No If yes, how long _____

Symptoms: (check all that apply)

☐ Headaches	☐ Difficulty concentrating
☐ Dizziness	☐ Irritability
☐ Memory problems	☐ Visual disturbances
☐ Balance problems	☐ Ringing in the ears
☐ Nausea/vomiting	Other _____

Symptom Score **A** (no current symptoms) **B** (one or more current symptoms)

Curent DATE/TIME: _____

Concussive Event DATE/TIME: _____

Time elapsed since this injury? _____ hours

Time elapsed since this injury and beginning of testing? _____ hours

Questions for seven day follow up interview (concussed group ONLY)

Rate your current level of pain TODAY -From 1 (nothing) to 10 (The worst pain you can imagine):

None 1 2 3 4 5 6 7 8 9 10 Severe

Symptoms: (check all that apply)

☐ Headaches	☐ Difficulty concentrating
☐ Dizziness	☐ Irritability
☐ Memory problems	☐ Visual disturbances
☐ Balance problems	☐ Ringing in the ears
☐ Nausea/vomiting	☐ Other _____

Note the order the tests were administered in 1 - 4:

☐ AHEAD ☐ ANAM ☐ ImPACT ☐ UPST

Appendix B – Unipedal Test Instructions

Unipedal Leg Stance

Subject ID: ☐☐☐☐☐☐☐ **Date:**

Read the following to the subject

1) During this test you will stand on your non-dominant foot. This is the opposite foot that you would kick a ball with.
2) The test will begin on a hard surface and then we will have you stand on a piece of foam.
3) Stand barefoot on your non-dominant foot, with the other leg raised so that the raised foot is near but not touching the ankle of your stance leg.
4) Prior to raising the limb, cross your arms over your chest, like this (demonstrate)
5) Focus on a spot on the wall at eye level in front of you, for the duration of the eyes open test.
6) I will use a stopwatch to measure the amount of time you are able to stand on one foot.
7) The time starts when you raise your foot off the floor.
8) The time ends when you either: (1) use your arms (i.e., uncrossed arms), (2) use your raised foot to touch the floor, (3) move your weight-bearing foot to maintain your balance (i.e., rotate foot on the ground) 4) open your eyes during the eyes closed test or (5) a maximum of 45 seconds had elapsed.
9) I will conduct this test 3 times in each position.

Dominate foot: (circle one) Left / Right	**Time 1**	**Time 2**	**Time 3**	**Average Time**
Hard surface eyes **open**				
Hard surface eyes **closed**				
Foam surface eyes **open**				
Foam surface eyes **closed**				

Appendix C – Recruitment Script Concussed Group

Recruitment Script for concussed group for ImPACT MIL v. ANAM4

To be read prior to persons who meet the prerequisites of having sustained a mTBI/concussion within the last 72 hours.

This will be read to those who have had sustained a concussion and were referred from the ED prior to collecting informed consent. It will be read in private to the concussed by a member of the research staff. Recruitment efforts will be brief consisting of a non-military civilian research assistant giving a brief (less than 5 minutes) speech asking for the concussed participation. The script for the speech will be read as follows:

> Hello my name is _____. I am here on behalf of the U.S. Army Medical Research and Material Command (USAMRMC) and I am recruiting volunteers to participate in a study on mTBI/concussion. There are currently two different neurocognitive tests used by the US Army today. One of them is the ANAM (automated neuropsychological assessment metric) and the other test is the ImPACT MIL (Immediate Post-Concussion Assessment and Cognitive Testing Military Version) currently being used to evaluate Special Forces troops. The study you are being asked to volunteer to participate in is designed to compare these two tests to see which of the tests is better suited for detecting the effects of acute concussion. For the purpose of this study we have asked the emergency department staff to aid in identifying those who have recently (within the last 72 hours) received a concussion. Everyone who has sustained a concussion is being asked to participate as part of the study group. If you choose to participate in the study it would take approximately one hour and will include the following: review of the Informed Consent sheet; a short screening questionnaire; two computerized neurocognitive tests, the ANAM and ImPACT; a short balancing test (UPST); and AHEAD M - 100, which involves the administration of a noninvasive, short EEG to monitor brain electrical signals. . There will be a break between each test and the balancing test will be conducted prior to the start of the second test. You will receive no financial benefit for your participation in this study but your time is greatly appreciated. Testing results will be reviewed by a neuropsychologist and if there are any abnormal results a write-up of the testing results will be sent to you for your medical records. At this time would you be interested in learning more about this study?

Those who elect to learn more about the study will be given the protocol ICD to review and ask questions about prior to testing if they agree to participate. Each member will be asked to complete the short screening questionnaire consisting of demographic information and the first page of the MACE (post-concussion symptom checklist). After each participant has completed the ICD and the questionnaire the first computerized test will be administered. Participants will complete the first test and be given a short break (10 mins.). During this time they may get

something to drink, use the restroom, smoke, stretch, etc. prior to starting the next test session each participant will be given a short balance test and then testing instruction will be given.

Appendix D – Recruitment Script Control Group

Recruitment Script for control group for ImPACT MIL v. ANAM4

To be read prior to service members already registered to take the ANAM as part of the SRP process.

Service members are tested in groups of 25 – 50 depending on the size of the testing location. Prior to testing, testing instruction are given to group members in a class like setting. Recruitment of potential control group members will be conducted at that time. Recruitment efforts will be brief consisting of a non-military civilian research assistant giving a brief (less than 5 minutes) speech to the group asking for participants. The script for the speech will be read as follows:

> Hello my name is _____. I am here on behalf of the U.S. Army Medical Research and Material Command (USAMRMC) and I am recruiting volunteers to participate in a study. There are currently two different neurocognitive tests used by the US Army today. One of them is the ANAM (automated neuropsychological assessment metric) which you will be taking today as part of the SRP process. The other test is the ImPACT MIL (Immediate Post-Concussion Assessment and Cognitive Testing Military Version) currently being used to evaluate Special Forces troops. The study you are being asked to volunteer to participate in is designed to compare these two tests to see which of the tests is better suited for detecting the effects of acute concussions in an active duty population. Everyone here is being asked to participate as part of the control group. Since everyone here is taking the ANAM the additional time I am asking for participation is an additional 40 minutes and will include the following: review of the Informed Consent sheet, a short screening questionnaire; two computerized neurocognitive tests, the ANAM and ImPACT; a short balancing test (UPST and AHEAD M - 100, which involves the administration of a noninvasive, short EEG to monitor brain electrical signals.. There will be a break between each test and the balancing test will be conducted prior to the start of the second test. You will receive no financial benefit for your participation in this study but your time is greatly appreciated. At this time who would be interested in learning more about this study?

Those who elect to learn more about the study will be asked to step across the hall into another testing room and will be given the protocol ICD to review and ask questions about prior to testing if they agree to participate. Each member will be asked to complete the short screening questionnaire consisting of demographic information and the first page of the MACE (post-concussion symptom checklist). After each participant has completed the ICD and the questionnaire the first computerized test will be administered. Participants will complete the first test and be given a short break (10 mins.) during this time they may get something to drink, use the restroom, smoke, stretch, etc. prior to starting the next test session each participant will be

given a short balance test and then testing instruction will be given. Participants will be free to continue with the SRP process once they have completed their second test.

Appendix – E BrainScope CEO IDE Letter

BRAINSCOPE

November 19, 2010

(b)(6) Ph.D.
Chief, Neurocognitive Assessment Branch,
(b)(6)

Dear Dr. (b)(6)

The BrainScope Ahead M-100 device is a non-invasive, "non-significant risk" (NSR) device [see 21 CFR 812.2(b) and FDA Guidance entitled, "Significant Risk and Non-significant Risk Medical Device Studies"]. This generic type of device, designed and marketed for EEG signal acquisition and processing, falls under "Class II" per 21 CFR 882.1400. FDA policy allows that EEG devices are specifically exempt from the need for an Investigational Device Exemption ODE) [see 21CFR812.2(c) and FDA Guidance for IRBs and Cls — 1998 Update at http://www.fda.goviocciohrthrbsidevices. html].

The BrainScope system consists of a handheld, battery operated device and a disposable non-invasive adhesive headset which contains electrodes that are similar to standard, off-the-shelf silver-silver chloride EEG electrodes. The data acquisition time for the BrainScope is 5 to 10 minutes total, depending mostly upon patient compliance. The device is intended as an assessment tool, not for continuous monitoring, thus the amount of time the electrodes reside on the patient's skin is minimal. The purpose of the clinical investigation is to collect brain electrical activity from human subjects. During clinical investigational use, the device will not provide any diagnostic or classification information and therefore will not impact upon patient care.

In summary, the BrainScope Ahead M-100 device used in this study does not pose a significant risk to the study subjects. Therefore, the study of the BrainScope device may be considered a non-significant risk study.

Sincerely,

Michael E. Singer, Ph.D.
Chief Executive Officer
BrainScope Company, Inc.

8120 Woodmont Ave.
Suite 250
Bethesda, MD 20814

(240) 752-7680
(800) 230-7573

www.BrainScop
e.com

Appendix F – Site Impact Statements

Date

IMPACT STATEMENT

Project Title: A Comparative Study: ImPACT MIL versus ANAM4 TBI MIL for Acute Concussion

Principal Investigator: (b)(6)

Service/Department: Brook Army Medical Center Department of Emergency Medicine

Assistance Requested: Requesting ED staff to aid in identifying and referring those patients with mTBI to ANAM research staff for participation in the current study. Study information will be given to the ED staff pertaining to inclusion/exclusion criteria and a member of the research team will be available to review the ICD, answer any questions pertaining to the study and schedule appointments as appropriate for the purpose of the study.

Total Number of Patients to be Studied: This study requires the participation of one hundred concussed (mTBI) patients from four Army Medical Centers. Participants will be recruited until the total number of concussed/mTBI patients has reached one hundred. There is no set number of patients required per location.

Number of Patients per Month: There is no set number of patients required per month. Data will be collected for a total of four months (120 days).

Length of Study: The study is expected to start in September 2010 data collection is expected to take no longer than four months (120 days) and analysis of data to take an additional six months (180 days) after data collection is complete for a total research time of 10 months (300 days).

(b)(6)

Date 09 JUNE 2010

(b)(6) Ph.D., LTC, MS (Clinical Neuropsychologist)

(b)(6)

☐ Disapproved, cannot support activity.

☒ Approved, no comment.

☐ Approved with comment.

Date:

(b)(6)

Date 7 Jun 2012

COL, MC

(b)(6)

Date: June 06, 2010

IMPACT STATEMENT

Project Title: A Comparative Study: ImPACT MIL versus ANAM4 TBI MIL for Acute Concussion

Principal Investigator: (b)(6)

Service/Department: Carl R. Darnall Army Medical Center Department of Emergency Medicine

Assistance Requested: Requesting ED staff to aid in identifying and referring those patients with mTBI to ANAM research staff for participation in the current study. Study information will be given to the ED staff pertaining to inclusion/exclusion criteria and a member of the research team will be available to review the ICD, answer any questions pertaining to the study and schedule appointments as appropriate for the purpose of the study.

Total Number of Patients to be Studied: This study requires the participation of one hundred concussed (mTBI) patients from four Army Medical Centers. Participants will be recruited until the total number of concussed/mTBI patients has reached one hundred. There is no set number of patients required per location.

Number of Patients per Month: There is no set number of patients required per month. Data will be collected for a total of four months (120 days).

Length of Study: The study is expected to start in September 2010 data collection is expected to take no longer than four months (120 days) and analysis of data to take an additional six months (180 days) after data collection is complete for a total research time of 10 months (300 days).

(b)(6)

(b)(6) PhD, LTC, MS (Clinical Neuropsychologist) Date 6/6/2010

(b)(6)

∀ Disapproved, cannot support activity.

∀ Approved, no comment.

∀ Approved with comment.

Template Version 2.1 1 Feb 2010

Date: June 06, 2010

(b)(6)

(b)(6) MD

(b)(6)

Date 11 June 10

Date: June 06, 2010

IMPACT STATEMENT

Project Title: A Comparative Study: ImPACT MIL versus ANAM4 TBI MIL for Acute Concussion

Principal Investigator: (b)(6)

Service/Department: Ft. Hood Soldier Readiness Process Site

Assistance Requested: Allow study staff ANAM test administrators to brief SRP soldiers prior to ANAM testing about the current study and recruit study participants. This may add an additional 40 minutes to the length of the participants testing time.

Total Number of Service Members to be Studied: This study requires the participation of two hundred control (non-concussed) active duty service members from two active duty SRP sites. Participants will be recruited until the total number of control/non-concussed service members has reached two hundred. There is no set number of service members required per location.

Number of Patients per Month: There is no set number of participants required per month. Data will be collected for a total of four months (120 days).

Length of Study: The study is expected to start in September 2010 data collection is expected to take no longer than four months (120 days) and analysis of data to take an additional six months (180 days) after data collection is complete for a total research time of 10 months (300 days).

(b)(6)

Date 30 June 10

(b)(6) Ph.D., LTC, MS (Clinical Neuropsychologist)
(b)(6)

☐ Disapproved, cannot support activity.

☑ Approved, no comment.

☐ Approved with comment.

Date: June 06, 2010

(b)(6)

JUL - 1 2010
Date:_____

(b)(6) LTC
(b)(6)

Date: 29 November 2010

IMPACT STATEMENT

Project Title: A Comparative Study: ImPACT MIL versus ANAM4 TBI MIL for Acute Concussion

Principal Investigator: (b)(6)
Associate Investigator:

Service/Department: Martin Army Community Hospital Department of Emergency Medicine

Assistance Requested: Requesting ED staff to aid in identifying and referring those patients with mTBI to ANAM research staff for participation in the current study. Study information will be given to the ED staff pertaining to inclusion/exclusion criteria and a member of the research team will be available to review the ICD, answer any questions pertaining to the study and schedule appointments as appropriate for the purpose of the study.

Total Number of Patients to be Studied: This study requires the participation of one hundred concussed (mTBI) patients from five Army Medical Centers. Participants will be recruited until the total number of concussed/mTBI patients has reached one hundred. There is no set number of patients required per location.

Number of Patients per Month: There is no set number of patients required per month. Data will be collected for a total of four months (120 days).

Length of Study: The study is expected to take no longer than four months (120 days) and analysis of data to take an additional six months (180 days) after data collection is complete for a total research time of 10 months (300 days).

(b)(6)

Date 29 NOV 10

(b)(6) Psy.D., CPT, MS (Clinical Psychologist)

(b)(6)

☐ Disapproved, cannot support activity.

☑ Approved, no comment.

☐ Approved with comment.

Template Version 2.1, 1 Feb 2010

Date 29 November 2010

(b)(6)

Date 11/24/10

(b)(6) MD

(b)(6)

Template Version 2.1 1 Feb 2010

Appendix G – Reportable Event Submission Form

U S Army Medical Research and Materiel Command
Office of Research Protections
HQ, USAMRMC Institutional Review Board

Reportable Event Submission Form

Purpose: *Use this form for the initial reporting of any study-related event that requires prompt reporting as per the "Responsibilities of the Principal Investigator in Human Subjects Research Investigator Agreement."*

Directions: *Place the cursor where you wish to type, and tab through the form. The completed form and any supporting documentation should be sent by email to* (b)(6)

Date of this report:

Person Reporting Event
Name:
Title/Position/Association with Study:
Phone number:
Email address:

Protocol Information
Protocol Number:
Study Title:
Name of Principal Investigator:

Event Information
Subject ID #:
Date of Event:
Time of Event:
Location of Event:

Event type(s) *Check all that apply*
- ☐ Unanticipated problem involving risks to subjects or others
- ☐ Serious adverse event
- ☐ Death
- ☐ Protocol deviation that may affect the safety or rights of subjects and/or the integrity of the study
- ☐ Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to research subject
- ☐ Incarceration of a subject
- ☐ Significant findings that might affect the willingness of subjects to enroll or to continue to take part
- ☐ Complaint by subject or other
- ☐ Noncompliance with the regulations or requirements
- ☐ Pending compliance inspection/visit by the FDA, OHRP, or other governmental agency
- ☐ Other event

Brief Description of Event (*who, what, why*)

Initial Actions Taken

Follow-up Actions to be Taken

FOR INTERNAL USE ONLY.

Report received by:

Date and time report received:

Report received via

- ☐ Phone call
- ☐ Email
- ☐ Fax

Routing

Name _____ Date: Initials:
Recommended Action:
Name: _____ Date: Initials:
Recommended Action:
Name: _____ Date: Initials:
Recommended Action:

Concurrence of HQ, MRMC IRB Approval Authority ☐ Yes ☐ No ☐ NA

_____ _____
(signature) *(date)*

Appendix H – Individual Investigator Agreement – (b)(6)

Department of Defense

Human Research Protection Program

DoD INDIVIDUAL INVESTIGATOR AGREEMENT

Part 1
AGREEMENT INFORMATION

This Department of the Defense (DoD) Individual Investigator Agreement describes the responsibilities of the individual who is engaged in human subject research and is not an employee of the assured institution, but is associated with the assured institution for the purpose of conducting research. This Agreement also describes the responsibilities of the assured institution. This Agreement, when signed, becomes part of the institution's Federal Assurance for the Protection of Human Research Subjects (e.g., DoD Assurance or Department of Health and Human Services (DHHS) Federalwide Assurance (FWA)).

A. Name of Investigator: (b)(6) **PhD**

B. Institution with the Assurance:

Name: **US Army Institute of Surgical Research**
DoD Assurance Number: **DOD A20104**
DHHS FWA Number [if applicable]: **FWA00009672**

C. Scope:

This Agreement applies to all research performed by this Investigator and supported by the Institution with the Assurance, unless specified below.

Limitation of Scope (if applicable):

This individual investigator agreement will apply to approved protocols conducted by Dr (b)(6) **until this agreement is rescinded.**

D. Effective Date:

This Agreement is effective as of the date signed by the DoD Component Designated Official and expires on the date listed in Part 4, paragraph D.

Part 2
INVESTIGATOR RESPONSIBILITIES

As the Investigator named above, I:

A. Have reviewed: a) *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*; b) the U.S. Department of Defense (DoD) regulations for the protection of human subjects at 32 Code of Federal Regulations, Part 219 (32 CFR 219) and DoD Directive 3216.02; c) the Assurance of the institution referenced above; d) the DoD Component policies identified in Part 3 of the DoD Assurance (if applicable); and e) the relevant institutional policies and procedures for the protection of human subjects.

B. Understand and accept the responsibility to comply with the standards and requirements stipulated in the above documents and to protect the rights and welfare of human subjects involved in research conducted under this Agreement.

C. Will comply with all other applicable federal, DoD, international, state, and local laws, regulations, and policies that provide protections for human subjects participating in research conducted under this Agreement.

D. Will complete any education and training required by the Institution and the IRB prior to initiating research covered under this Agreement (attach documentation).

E. Will abide by all determinations of the Institutional Review Board(s) (IRB) designated under the Institution's Assurance and will accept the final authority and decisions of the IRB, including but not limited to directives to terminate my participation in designated research activities.

F. Will not enroll subjects or start research activities under this Agreement prior to its review and approval by the IRB and the Institution.

G. Will comply with requirements from the IRB when responsible for enrolling subjects, to include obtaining, documenting, and maintaining records of informed consent for each such subject or each subject's legally authorized representative as required under DoD regulations at 32 CFR 219.

H. Acknowledge and agree to cooperate with the IRB for initial and continuing review, report for the research referenced above, and provide all information requested by the IRB or Institution in a timely fashion.

I. Will seek prior IRB review and approval for all proposed changes in the research except where necessary to eliminate apparent immediate hazards to subjects or others.

J. Will report immediately to the IRB a) unanticipated problems involving risks to subjects or others and b) serious or continuing non-compliance

K. Will comply with recordkeeping requirements for research protocols referenced above.

L. Will make all other notifications as specified by the IRB and the Institution.

M. Acknowledge my primary responsibility for safeguarding the rights and welfare of each research subject, and that the subject's rights and welfare will take precedence over the goals and requirements of the research.

Part 3
ASSURED INSTITUTION'S RESPONSIBILITIES

This Institution will apply the terms of its assurance to the Investigator and the research as specified in the scope of this Agreement, Part 1.

Part 4
AGREEMENT BETWEEN AN INVESTIGATOR AND AN ASSURED INSTITUTION

The Investigator or an official of the assured Institution may unilaterally terminate this agreement upon written notification to other signatories.

A. Investigator:

I understand my responsibilities as described in this Agreement and the policies referenced in Part 2A above. I acknowledge and accept my responsibility for protecting the rights and welfare of human research subjects and for complying with all applicable provisions of the Institution's Assurance.

Signature: (b)(6) Date: 18 MAR 2011

Name: (b)(6) PhD
Rank/Grade: NSPS YA-03
Title: Clinical Neuropsychologist
Telephone number: (b)(6)
FAX number: (b)(6)
Email address: (b)(6)
Mailing Address: (b)(6), Ph.D., (Clinical Neuropsychologist)
(b)(6)

B. Acknowledgement by Investigator's Employer (or DoD Supervisor if DoD Employee):

I am aware that my employee is entering into this agreement.

Signature: (b)(6) Date: 19 Mar 11

Name: (b)(6) DPT, OCS
Rank/Grade: COL
(b)(6)

C. Institutional Official of the Assured Institution:

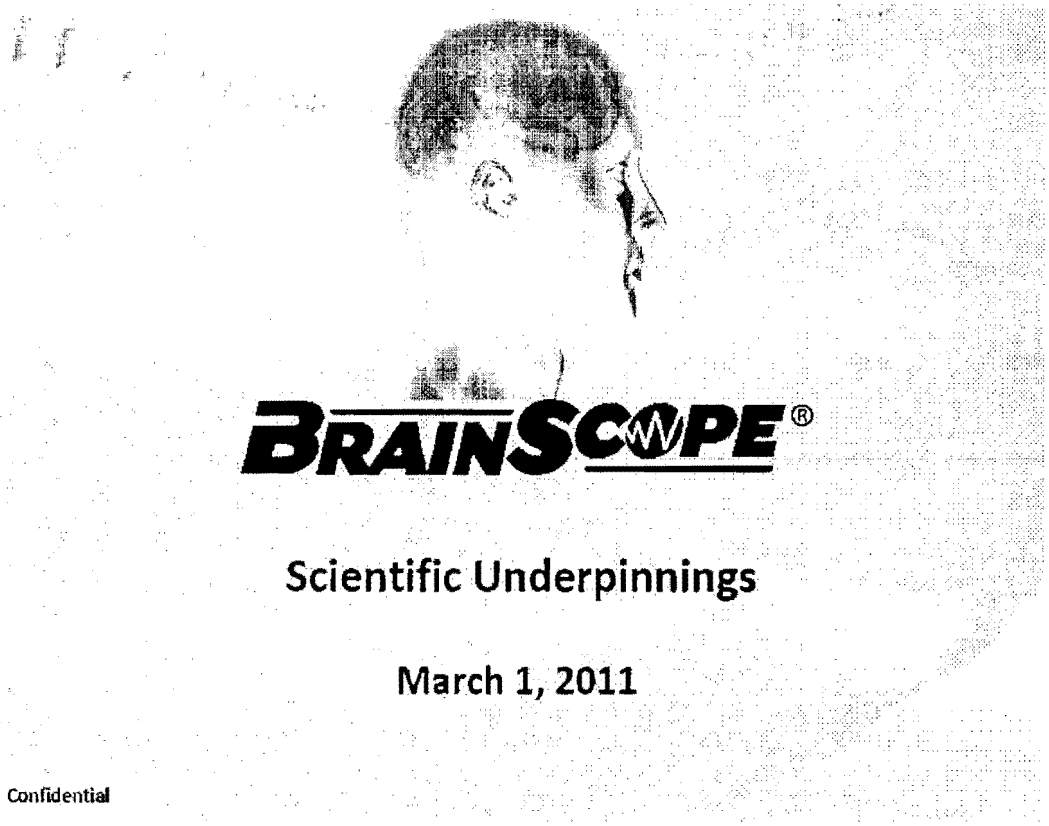
Acting in an authorized capacity on behalf of this Institution and with an understanding of the Institution's responsibilities under the Institution's Assurance, I will provide oversight of the Investigator and the research conducted under this Agreement.

Signature: (b)(6) Date: MAR 2 3 2011

Name: (b)(6)
Rank/Grade: Colonel, Medical Corps
Title: Commander
Telephone number: (b)(6)
FAX number: (b)(6)
Email address: (b)(6)

Mailing Address: (b)(6)

Appendix I – BrainScope Scientific Overview



Confidentiality

THIS DOCUMENT CONTAINS CONFIDENTIAL, PROPRIETARY AND/OR TRADE SECRET INFORMATON OWNED BY BRAINSCOPE COMPANY, INC. (BRAINSCOPE).

ANY PERSON ACCEPTING THIS DOCUMENT AND/OR INFORMATION AGREES TO MAKE NO DISCLOSURE, USE OR DUPLICATION THEREOF EXCEPT AS AUTHORIZED IN WRITING BY THE BRAINSCOPE MANAGEMENT. UPON REQUEST OF BSC, THIS DOCUMENT MUST BE RETURNED OR DESTROYED.

The BrainScope Ahead™ M-100 System is an Investigational Device only, for use only by qualified personnel, and the use of the device remains limited by U.S. Federal Law to investigational uses only. BrainScope makes no representations regarding the device's safety or efficacy.

(b)(4)

(b)(4)

(b)(4)

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(b)(4)

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